



# UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE

United States Patent and Trademark Office

Address: COMMISSIONER FOR PATENTS

P.O. Box 1450

Alexandria, Virginia 22313-1450

www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
-----------------	-------------	----------------------	---------------------	------------------

10/517,214

03/01/2005

Tsuyoshi Mackawa

10525.0004

7396

22852

7590

09/17/2008

FINNEGAN, HENDERSON, FARABOW, GARRETT & DUNNER

LLP

901 NEW YORK AVENUE, NW

WASHINGTON, DC 20001-4413

EXAMINER

JABLE, CECILIA M

ART UNIT

PAPER NUMBER

1624

MAIL DATE

DELIVERY MODE

09/17/2008

PAPER

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

### Office Action Summary

**Application No.**

10/517,214

**Applicant(s)**

TSUYOSHI MAEKAWA, ET AL.

**Examiner**

Cecilia M. Jaisle

**Art Unit**

1624

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --  
**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

- 1) ☒ Responsive to communication(s) filed on 03 July 2008.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

- 4) ☒ Claim(s) 1-3,5-15, 17-21, 23-27, 30 and 31 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1-3,5-12, 14, 15, 18-21, 23-27, 30 and 31 is/are rejected.
- 7) ☒ Claim(s) 13 and 17 is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

**Application Papers**

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

- 12) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☒ All b) ☐ Some \* c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
  2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  3. ☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO/SB/08)  
Paper No(s)/Mail Date \_\_\_\_\_
- 4) ☐ Interview Summary (PTO-413)  
Paper No(s)/Mail Date \_\_\_\_\_
- 5) ☐ Notice of Informal Patent Application
- 6) ☐ Other: \_\_\_\_\_

**DETAILED OFFICE ACTION**

***Rejections Under 35 USC 112***

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 8, 20, 21, 23-27, 30 and 31 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claims contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

The specification as filed does not support the recitation of R2 and R3 as "optionally having 1 to 3 substituents," broadly, when the specification (p. 37, l. 15 – p. 38, l. 9) recites a limited group of specific substituents. This is a new matter rejection.

Claims 20, 21, 23-27 and 30 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for hypoglycemic and hypolipidemic actions in obese and non-insulin dependent type 2 diabetic mice, plasma anti-arteriosclerosis index-enhancing action in obese and non-insulin dependent type 2 diabetic mice, *in vitro* PPAR $\gamma$ -RXR $\alpha$  heterodimer ligand activity, and *in vitro* PPAR $\alpha$ -RXR $\alpha$  heterodimer ligand activity, does not reasonably provide enablement for treatment of type 1 diabetes, type 2 diabetes or gestational diabetes (claim 20),

treatment of hyperlipidemia in any mammal in need thereof (claim 21), treatment of impaired glucose tolerance in a mammal (claim 23), regulating retinoid-related function in a mammal (claims 24-26), improving an insulin resistance in a mammal (claim 27), or modulating a GPR40 receptor function in a mammal (claim 30). The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The specification does not provide competent evidence that the instantly disclosed tests are predictive of all uses disclosed and embraced by the claims. Substantiation of utility and its scope is required when utility is "speculative," "sufficiently unusual" or not provided. See *Ex parte Jovanovics, et al.*, 211 USPQ 907, 909 (BPAI 1981). Also, note *Hoffman v. Klaus*, 9 USPQ2d 1657 (BPAI 1988) and *Ex parte Powers*, 220 USPQ 924 (BPAI 1982) regarding types of testing needed to support *in vivo* uses.

Applicants' attention is drawn to the Revised Interim Utility and Written Description Guidelines, at 66 FR 1092-1099 (2001), emphasizing that "a claimed invention must have a specific and substantial utility." See also MPEP 2163, *et. seq.* This application's disclosure is insufficient to enable the instantly claimed methods. The state of the art indicates the requirement for undue experimentation.

Many factors require consideration when determining whether sufficient evidence supports a conclusion that a disclosure satisfies the enablement requirement and whether any necessary experimentation is "undue." MPEP 2164.01(a). These factors include: (1) the claim breadth; (2) the nature of the invention; (3) the state of the prior art; (4) the level of predictability in the art; (5) the amount of direction provided by the

inventor; (6) the presence of working examples; and (7) the quantity of experimentation needed to make or use the invention based on the content of the disclosure. *In re Wands*, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)(reversing the PTO's determination that claims directed to methods for detection of hepatitis B surface antigens did not satisfy the enablement requirement). See also *In re Goodman* 29 USPQ2d 2010, 2013 (Fed. Cir. 1993). Application of these factors to the present application supports the determination that the present disclosure fails to satisfy the enablement requirement:

(1) Breadth of claims.

(a) Scope of the methods. The method claims cover the use of substituted pyrazoles and pharmaceutically acceptable salts.

(b) Scope of the disorders covered. The scope of the disorders said to be treated by the claimed methods are highlighted above.

**Impaired Glucose Tolerance (IGT)** is a pre-diabetic state of dysglycemia associated with insulin resistance and increased risk cardiovascular pathology. IGT may precede type 2 diabetes mellitus by many years. IGT is a mortality risk factor. The risk of progression to diabetes and development of cardiovascular disease is greater than for impaired fasting glycaemia. Although some drugs can delay diabetes onset, lifestyle modifications play a greater role in diabetes prevention. Applicants fail to describe how the present methods assist in such lifestyle modification.

The primary treatment for insulin resistance is exercise and weight loss. In some individuals, a low-glycemic index or a low-carbohydrate diet may also help. Both metformin and the thiazolidinediones improve insulin resistance, but are only appro-

ved therapies for type 2 diabetes, not insulin resistance, *per se*. By contrast, growth hormone replacement therapy may be associated with increased insulin resistance. The *Diabetes Prevention Program* showed exercise and diet were nearly twice as effective as metformin at reducing the risk of progressing to type 2 diabetes. Applicants fail to describe how the present methods assist in exercise and weight loss.

In regard to claims 24-26 it is not understood what is intended by "regulating retinoid-related function in a mammal." The specification states:

"The term "retinoid-related receptor" used here is classified as nuclear receptors, and is a DNA-binding transcription factor whose ligand is a signal molecule such as oil-soluble vitamins, etc., and may be any of a monomer receptor, a homodimer receptor and a heterodimer receptor."

A "signal molecule" could be pretty much anything. There is no clear way to determine what is and is not covered by these claims.

(2) The nature of the invention and predictability in the art: Therapeutic use of substituted pyrazoles and salts in preventing and treating disorders recited above. It is well established that "the scope of enablement varies inversely with the degree of unpredictability of the factors involved" and physiological activity is generally considered to be an unpredictable factor. *In re Fisher*, 166 USPQ 18, 24 (CCPA 1970).

(3) Direction or Guidance: That provided is very limited. Dosage range information is meager; it would require extensive experimentation to determine specific dosage for a specific recited disorder, mode of administration and therapeutic regimen. The dosage is generic; the same for many disorders the specification covers. No specific direction or guidance gives a regimen or dosage effective specifically for various

types of diseases. No dosage or therapeutic regimen is present to direct the skilled artisan to protect a potential host from all named disorders.

(4) State of the Prior Art: Kebede, et al., Diabetes 57:2432-2437, 2008 reports research that raises "doubts on the validity of a therapeutic approach based on GPR40 antagonism for the treatment of type 2 diabetes.

Calkin, et al., Nephrol. Dial. Transplant. (2006), 21:2399-2405, points to the need for further research:

In summary, the PPAR-alpha agonist, gemfibrozil, the PPAR-gamma, rosiglitazone and the PPAR-alpha/gamma co-agonist, compound 3q, have equivalent renoprotective actions in experimental diabetes, over and above effects on plasma, glucose, blood pressure or lipid levels. This finding is consistent with the important role of the PPAR signaling system in diabetic complications. Moreover, these benefits correlate with the direct anti-atherogenic effects of PPAR agonists observed in the diabetic vasculature. The clinical relevance of this finding remains to be established, given the negative effects of the dual agonist, muraglitazar in patients with diabetes and equivocal outcomes with side effects observed in the recent FIELD and proACTIVE studies.

Wieser, et al., PPAR Res. 2008; 2008: 527048, reports alarming findings:

Ongoing basic studies have elucidated the metabolic, antiinflammatory, and angiogenic benefits of PPAR $\alpha$ / $\beta/\delta$  and PPAR $\gamma$ / $\beta/\delta$  dual agonists and PPAR pan agonists for treatment purposes. However, some experimental and clinical data have uncovered unfortunate side effects of PPAR ligands, including cancer progression and increased cardiac event rates. New generations of PPAR modulators are under development and these promise to be more receptor-specific, and hopefully will activate only a specific subset of target genes and metabolic pathways to reduce untoward side effects. The potential role of PPARs in regulation of inflammation and angiogenesis is intriguing and warrants further studies. We submit that PPAR agonists may become beneficial drugs for pregnancy-specific diseases, once their risks have been fully evaluated.

Ability of claimed methods to treat all disorders asserted above remains open to proof. A skilled person in this art would need undue experimentation.

(5) Working Examples: The disclosure fails to correlate the test results in the specification to the treatments construed by the claims. The specification merely prophesies that the methods will treat prevent all disorders mentioned above.

The specification states that the methods treat all claimed disorders, for which Applicants provide insufficient evidence. Applicants have not provided competent evidence of known tests highly predictive for all disorders embraced by the claim language for the intended host. Pharmacological activity in general is unpredictable. In applications involving physiological activity, such as the present,

"The first paragraph of 35 U.S.C. 112 effectively requires that the scope of the claims must bear a reasonable correlation to the scope of enablement provided by the specification to persons of ordinary skill in the art."

*Plant Genetic Syst. v. DeKalb Genetics*, 65 USPQ2d 1452, 1456 (Fed. Cir. 2003). "[T]he scope of enablement obviously varies inversely with the degree of unpredictability of the factors involved." *In re Fisher*, 166 USPQ 18 (CCPA 1970).

(6) Skill of those in the art: See the discussion above of Kebede, Calkin and Wieser. The state of the art supports that successful treatment and prevention of all disorders recited is a subject for further investigation.

(7) The quantity of experimentation needed: Based on the disclosure content, to use the invention would place an undue burden on one skilled in the pharmaceutical arts, since the disclosure gives the skilled artisan inadequate guidance regarding pharmaceutical use, for the reasons stated above.



The discussion of the above factors demonstrates that the present application sufficiently lacks enablement of the present claims. In view of the breadth of the claims, the pharmaceutical nature of the invention, the unpredictability of relationship between 5-HT<sub>2</sub> receptor antagonist activity and treatment and prevention of all disorders, one of ordinary skill in this art would have to undergo an undue amount of experimentation to use the instantly claimed invention commensurate in scope with the claims.

MPEP 2164.01(a) states,

A conclusion of lack of enablement means that, based on the evidence regarding each of the above [Wand] factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. *In re Wright*, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993).

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-3, 5-7, 9-12, 14, 15, 18-21, 23-27, 30 and 31 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Xb and Yb cannot both simultaneously be a bond without intervening atoms. Applicants state that the term "bond" is an expression indicating the identified moiety is not present. If any moiety identified as a "bond" is not present, the remaining portions of the molecule on either side are separate moieties and do not form a single compound.

### ***Request for Foreign Priority***

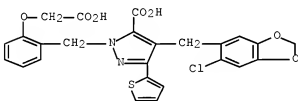
If Applicants wish to obtain benefit of their foreign priority applications to overcome any rejections below, certified English translations thereof must be filed. Until such translations are filed, this application has a May 22, 2003 effective filing date.

### ***Rejections Under 35 USC 102***

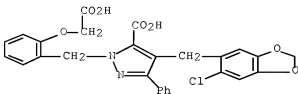
The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

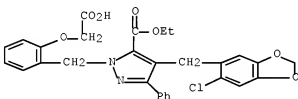
Claims 1, 2, 7, 9, 11, 12, 14, 15, 18 and 19 are rejected under 35 U.S.C. 102(b) over Zhang, et al., Bioorg. & Med. Chem. Letters (2000), 10(22), 2575-2578, describing RN 190321-43-8, 1H-Pyrazole-5-carboxylic acid, 1-[[2-(carboxymethoxy)phenyl]methyl]-4-[(6-chloro-1,3-benzodioxol-5-yl)methyl]-3-(2-thienyl)-,



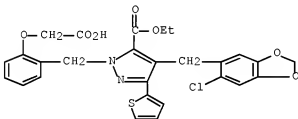
RN 321200-99-1, 1H-Pyrazole-5-carboxylic acid, 1-[[2-(carboxymethoxy)phenyl]methyl]-4-[(6-chloro-1,3-benzodioxol-5-yl)methyl]-3-phenyl-,



RN 321201-18-7, 1H-Pyrazole-5-carboxylic acid, 1-[[2-(carboxymethoxy)phenyl]methyl]-4-[(6-chloro-1,3-benzodioxol-5-yl)methyl]-3-phenyl-, 5-ethyl ester,

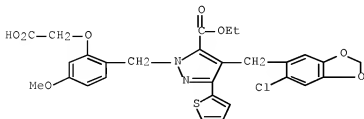


RN 321201-21-2, 1H-Pyrazole-5-carboxylic acid, 1-[[2-(carboxymethoxy)phenyl]methyl]-4-[(6-chloro-1,3-benzodioxol-5-yl)methyl]-3-(2-thienyl)-, 5-ethyl ester,



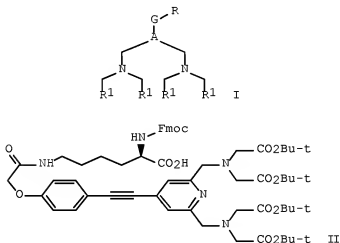
, and

RN 321201-22-3, 1H-Pyrazole-5-carboxylic acid, 1-[[2-(carboxymethoxy)-4-methoxyphenyl]methyl]-4-[(6-chloro-1,3-benzodioxol-5-yl)methyl]-3-(2-thienyl)-, 5-ethyl ester,



as potent nonpeptide endothelin antagonists.

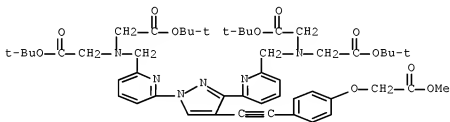
Claims 1-3, 11, 12, 14 and 15 are rejected under 35 U.S.C. 102(b) as being unpatentable over Takalo, et al., US 6080839, issued 20000627, describing



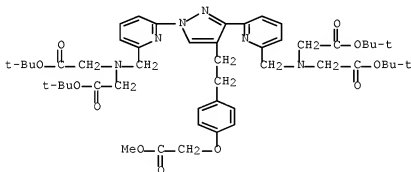
pyridinediylbis(methylenenitrilo)tetrakisacetic acid labeling reactants, suitable for fluorescent labeling of biospecific binding reactants in solid-phase synthesis. labeling reactants (I) [wherein A = a bivalent aromatic structure capable of absorbing light or energy and transferring excitation energy to a lanthanide ion after the product made by solid-phase synthesis has been released from the used solid support, deprotected, and converted to a lanthanide chelate; R = -Z(G<sub>1</sub>-NH-X)G<sub>2</sub>-E; X = a transient protecting group, e.g. 2-(4-nitrophenyl)sulfonyl)ethoxycarbonyl, trityl, 4-methoxytrityl, 4,4'-dimethoxytrityl, BOC, Fmoc; E = a carboxylic acid, its salt, active ester (e.g. N-hydroxysuccinimido, nitrophenol, 2,4-dinitrophenol, or pentafluorophenol), or halide; Z = bridge point; G = bridge between A and Z; G<sub>1</sub> = bridge between NH and Z; G<sub>2</sub> = bridge

between E and Z; R1 = CO2R2; R2 = alkyl or (un)substituted Ph or benzyl] are particularly useful in labeling small molecule. See the specific examples:

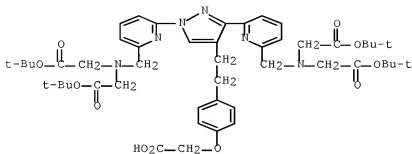
RN 253137-97-2, Glycine, N,N'-[[4-[4-(2-methoxy-2-oxoethoxy)phenyl]ethynyl]-1H-pyrazole-1,3-diyl]bis(6,2-pyridinediylmethylene))bis[N-2-(1,1-dimethylethoxy)-2-oxoethyl]-, bis(1,1-dimethylethyl) ester,



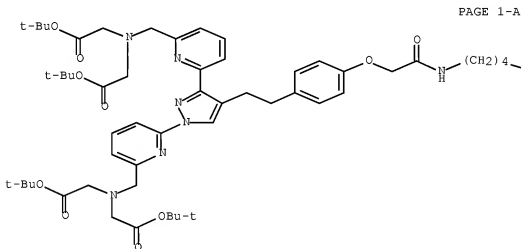
RN 253137-98-3, Glycine, N,N'-[[4-[2-[4-(2-methoxy-2-oxoethoxy)phenyl]ethyl]-1H-pyrazole-1,3-diyl]bis(6,2-pyridinediylmethylene))bis[N-2-(1,1-dimethylethoxy)-2-oxoethyl]-, bis(1,1-dimethylethyl) ester,



RN 253137-99-4, Glycine, N,N'-[[4-[2-[4-(carboxymethoxy)phenyl]ethyl]-1H-pyrazole-1,3-diyl]bis(6,2-pyridinediylmethylene))bis[N-2-(1,1-dimethylethoxy)-2-oxoethyl]-, 1,1'-bis(1,1-dimethylethyl) ester,

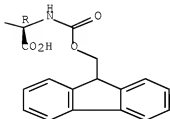


RN 253137-93-8, D-Lysine, N6-[[4-[2-[1,3-bis[6-[[bis[2-(1,1-dimethylethoxy)-2-oxoethyl]amino]methyl]-2-pyridinyl]-1H-pyrazol-4-yl]ethyl]phenoxy]acetyl]- N2-[(9H-fluoren-9-ylmethoxy)carbonyl]-,

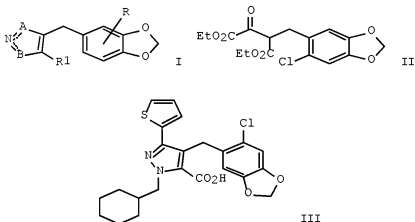


PAGE 1-A

PAGE 1-B

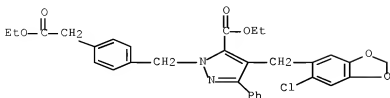


Claims 1, 2, 5, 7, 9, 11, 12, 14, 15 and 19 are rejected under 35 U.S.C. 102(b) as being unpatentable over Didierlaurent, et al., US 5942622, issued 19990824, describing

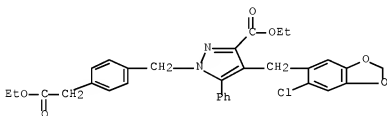


Compounds I [1 of A and B = NR<sub>2</sub>, the other = CR<sub>3</sub>, so that A = NR<sub>2</sub> and R<sub>2</sub> = alkyl, or A = CR<sub>3</sub> and R<sub>3</sub> = Ph, thienyl, or pyridyl; and B = NR<sub>2</sub> and R<sub>2</sub> = cyclohexylalkyl, or B = CR<sub>3</sub> and R<sub>3</sub> = alkylthio; R<sub>1</sub> = CO<sub>2</sub>H; R = halogen] and isomers and salts are disclosed. The compounds are endothelin receptor antagonists, useful for inhibiting effects of endothelin, e.g., vasoconstriction and hypertension. In assays for binding to endothelin A and B receptors *in vitro*, compounds III had IC<sub>50</sub> values of 1.1 and 1.7 nM, respectively. See the examples:

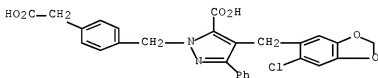
RN 190321-70-1, 1H-Pyrazole-5-carboxylic acid, 4-[(6-chloro-1,3-benzodioxol-5-yl)methyl]-1- [[4-(2-ethoxy-2-oxoethyl)phenyl]methyl]-3-phenyl-, ethyl ester,



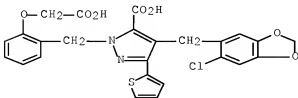
RN 190321-71-2, 1H-Pyrazole-3-carboxylic acid, 4-[[6-chloro-1,3-benzodioxol-5-yl)methyl]-1- [[4-(2-ethoxy-2-oxoethyl)phenyl]methyl]-5-phenyl-, ethyl ester,



RN 190321-37-0, 1H-Pyrazole-5-carboxylic acid, 1-[[4-(carboxymethyl)phenyl]methyl]-4-[[6-chloro-1,3-benzodioxol-5-yl)methyl]-3-phenyl-,

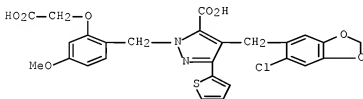


RN 190321-43-8, 1H-Pyrazole-5-carboxylic acid, 1-[[2-(carboxymethoxy)phenyl]methyl]-4-[[6-chloro-1,3-benzodioxol-5-yl)methyl]-3-(2-thienyl)-,

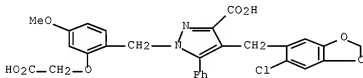




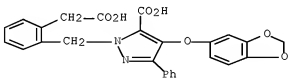
RN 190321-45-0, 1H-Pyrazole-5-carboxylic acid, 1-[[2-(carboxymethoxy)-4-methoxyphenyl]methyl]-4-[[6-chloro-1,3-benzodioxol-5-yl)methyl]-3-(2-thienyl)-,



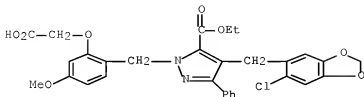
Claims 1, 2, 5, 7, 9, 11, 12, 14, 15, 18 and 19 are rejected under 35 U.S.C. 102(b) as being unpatentable over Fortin, et al., WO 9612706, published 19960502, describing RN 179109-28-5, 1H-Pyrazole-3-carboxylic acid, 1-[[2-(carboxymethoxy)-4-methoxyphenyl]methyl]-4-[[6-chloro-1,3-benzodioxol-5-yl)methyl]-5-phenyl-,



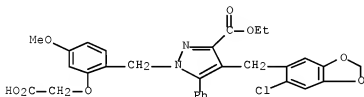
RN 179109-33-2, 1H-Pyrazole-5-carboxylic acid, 4-(1,3-benzodioxol-5-yloxy)-1-[[2-(carboxymethyl)phenyl]methyl]-3-phenyl-,



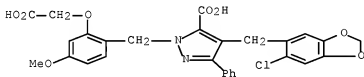
RN 179110-55-5, 1H-Pyrazole-5-carboxylic acid, 1-[[2-(carboxymethoxy)-4-methoxyphenyl]methyl]-4-[[6-chloro-1,3-benzodioxol-5-yl)methyl]-3-phenyl-, 5-ethyl ester,



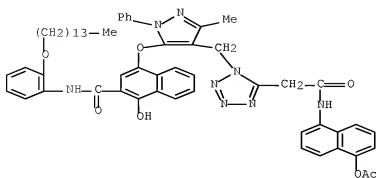
RN 179110-56-6, 1H-Pyrazole-3-carboxylic acid, 1-[[2-(carboxymethoxy)-4-methoxyphenyl]methyl]-4-[(6-chloro-1,3-benzodioxol-5-yl)methyl]-5-phenyl-, 3-ethyl ester,



RN 179109-27-4, 1H-Pyrazole-5-carboxylic acid, 1-[[2-(carboxymethoxy)-4-methoxyphenyl]methyl]-4-[(6-chloro-1,3-benzodioxol-5-yl)methyl]-3-phenyl-,

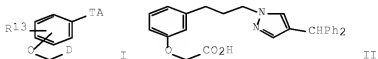


Claims 1, 2, 5, 7, 8, 12, 14 and 15 are rejected under 35 U.S.C. 102(b) as being unpatentable over Odenwaelder, et al., US 5441857, issued 19950815, describing RN 167307-81-5, 1H-Tetrazole-5-acetamide, N-[5-(acetyloxy)-1-naphthalenyl]-1-[[5-[[4-hydroxy-3-[[[2-(tetradecyloxy)phenyl]amino]carbonyl]-1-naphthalenyl]oxy]-3-methyl-1-phenyl]-1H-pyrazol-4-yl]methyl]-,

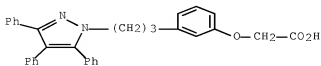


, as a photographic coupler.

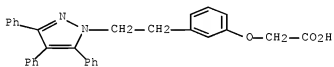
Claims 1-3, 5, 7, 9, 11, 12, 14, 15, 18 and 19 are rejected under 35 U.S.C. 102(b) over Hamanaka, et al., US 5378716, issued 19950103, describing



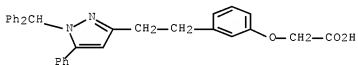
The compounds I [A = heterocyclyl, carboxylate, (un)substituted CH<sub>2</sub>NH<sub>2</sub>, etc.; D = CO<sub>2</sub>R<sub>10</sub>, CONR<sub>11</sub>R<sub>12</sub>; R<sub>10</sub> = H, C<sub>1</sub>-12 alkyl; R<sub>11</sub>, R<sub>12</sub> = H, C<sub>1</sub>-4 alkyl; R<sub>13</sub> = H, C<sub>1</sub>-4 alkyl, C<sub>1</sub>-4 alkoxy, NO<sub>2</sub>; T = direct bond, C<sub>1</sub>-6 alkylene, C<sub>2</sub>-6 alkenylene, O(CH<sub>2</sub>)<sub>s</sub>; s = 2-4], useful to treat thrombosis, arteriosclerosis, ischemic heart disease, gastric ulcer or hypertension. Me 3-[3-(4-diphenylmethylpyrazol-1-yl)propyl]phenoxyacetate was hydrolyzed, producing pyrazole derivative II which demonstrated a 50% human blood platelet aggregation inhibitory concentration of 0.42 μM. See the example RN 153183-92-7, Acetic acid, [3-[3-(3,4,5-triphenyl-1H-pyrazol-1-yl)propyl]phenoxy]-,



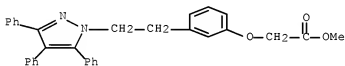
Claims 1-3, 5, 7, 9, 11, 12, 14, 15, 18 and 19 are rejected under 35 U.S.C. 102(b) over Meanwell, et al., J. Med. Chem. (1992), 35(19), 3498-512, describing :  
RN 143547-18-6, Acetic acid, [3-[2-(3,4,5-triphenyl-1H-pyrazol-1-yl)ethyl]phenoxy]-,



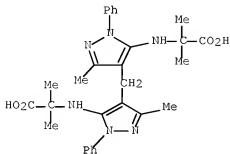
RN 143547-20-0, Acetic acid, [3-[2-[1-(diphenylmethyl)-5-phenyl-1H-pyrazol-3-yl]ethyl]phenoxy]-,



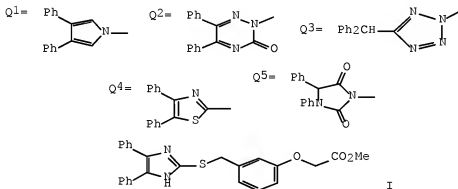
RN 143547-19-7, Acetic acid, [3-[2-(3,4,5-triphenyl-1H-pyrazol-1-yl)ethyl]phenoxy]-, methyl ester,



Claims 1, 2, 5, 7, 11, 12, 14, 15 and 19 are rejected under 35 U.S.C. 102(b) over Dorn, et al., DD 294481, published 19911002, describing RN 139304-23-7, Alanine, N,N'-[methylenebis(3-methyl-1-phenyl-1H-pyrazole-4,5-diyl)]bis[2-methyl-,

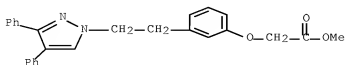


Claims 1-3, 5, 7, 9, 11, 12, 14, 15, 18 and 19 are rejected under 35 U.S.C. 102(b) as being unpatentable over Meanwell, et al., US 4956379, issued 19900911, describing



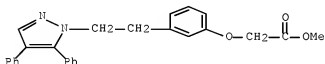
in which  $X(CH_2)_nCO_2R$  ( $R = H$ , alkyl, alkali metal;  $n = 6-9$ ;  $X = Q1-Q5$ , etc.), and related compounds. I inhibited aggregation of human platelets. See examples:

RN 131362-16-8, Acetic acid, [3-[2-(3,4-diphenyl-1H-pyrazol-1-yl)ethyl]phenoxy]-, methyl ester,

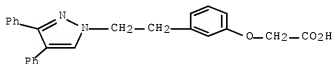


Art Unit: 1624

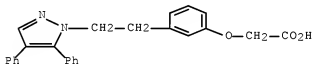
RN 131362-17-9, Acetic acid, [3-[2-(4,5-diphenyl-1H-pyrazol-1-yl)ethyl]phenoxy]-, methyl ester,



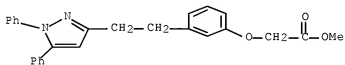
RN 131362-18-0, Acetic acid, [3-[2-(3,4-diphenyl-1H-pyrazol-1-yl)ethyl]phenoxy]-,



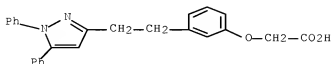
RN 131362-19-1, Acetic acid, [3-[2-(4,5-diphenyl-1H-pyrazol-1-yl)ethyl]phenoxy]-,



RN 131362-20-4, Acetic acid, [3-[2-(1,5-diphenyl-1H-pyrazol-3-yl)ethyl]phenoxy]-, methyl ester,

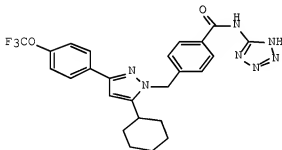
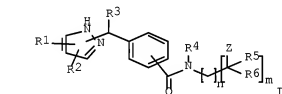


RN 131362-21-5, Acetic acid, [3-[2-(1,5-diphenyl-1H-pyrazol-3-yl)ethyl]phenoxy]-,



(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

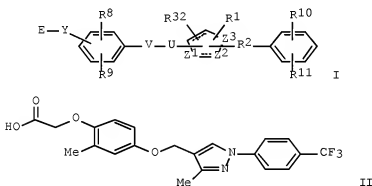
Claims 1-3, 5, 7, 9, 11, 12, 14, 15 and 18-20 are rejected under 35 U.S.C. 102(e) over Parmee, et al., WO 2004069158, entitled to the date of Jan. 27, 2003, describing



The title compounds [I; R1 = alkyl, alkenyl, aryl, etc.; R2 = H, R1; R3, R4 = H, alkyl; R5 = H, F; R6 = H, OH, F, alkyl; or R5 and R6 together represent oxo; m = 0-2; n = 0-6;

with provisos] are glucagon receptor antagonists and are useful to treat or delay onset of type 2 diabetes mellitus. See the specific examples.

Claims 1-3, 5, 7, 9, 11, 12, 14, 15 and 18-20 are rejected under 35 U.S.C. 102(e) over Conner, et al., WO 2004063166, entitled to the date of Jan. 6, 2003, describing



The title pyrazoles [wherein R<sup>1</sup> = H, (un)substituted alkyl, alkenyl, (hetero)aryl(alkyl), arylheteroalkyl, cycloalkylaryl(alkyl); R<sup>2</sup> = bond, (hetero)alkyl; R<sup>8</sup> = H, alkyl, alkylenyl, halo; R<sup>9</sup> = H, (un)substituted alkyl, alkylenyl, halo, aryl(alkyl), heteroaryl, allyl, alkoxy, alkylthio, etc.; R<sup>10</sup>, R<sup>11</sup> = independently H, OH, CN, NO<sub>2</sub>, halo, oxo, (un)substituted (halo)alkyl, alkoxy, cycloalkyl, (hetero)aryl(alkyl), cycloalkylaryl(alkyl), aryloxy, acyl, carboxy, amino, sulfamoyl, etc.; R<sup>32</sup> = bond, H, halo, (halo)alkyl, alkylloxo; E = (un)substituted carboxy(methyl), tetrazolyl(methyl), nitriloalkyl, carboxamido(methyl), sulfonamido(methyl); U = (un)substituted aliphatic linker wherein one C of the linker is optionally replaced with O, NH, or S; X = bond, O, S, SO<sub>2</sub>, NH; Y = bond, CH<sub>2</sub>, NH; Z<sup>1</sup>, Z<sup>2</sup> = independently N, O, C, with the proviso that at least one of Z<sup>1</sup> and Z<sup>2</sup> = N; Z<sup>3</sup> = N,



O, C; or stereoisomers, pharmaceutically acceptable salts, are peroxisome proliferator activated receptor modulators. Compounds of formula I and their pharmaceutical compositions are expected to be effective in treating metabolic disorders, diabetes mellitus, atherosclerosis and cardiovascular disorders. See the specific examples.

### ***Objectionable Claims***

Claims 13 and 17 are objectionable because they are dependent on a rejected claim. They would be allowed if rewritten to overcome the rejections of the claims on which they depend.

### ***Conclusion***

Applicant's amendment necessitated the new grounds of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Cecilia M. Jaisle, J.D. whose telephone number is 571-272-9931. The examiner can normally be reached on Monday through Friday; 8:30 am through 5:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James O. Wilson can be reached on 571-272-0661. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Cecilia M. Jaisle, J.D.

9/10/2008

**/James O. Wilson/**

**Supervisory Patent Examiner, Art Unit 1624**